Supplemental materials

Assessment of biomarkers of CVD risk in the Moli-sani Study

Blood samples were collected at baseline (2005-2010) in participants who had fasted overnight and had refrained from smoking for at least 6 h. Lipids (total cholesterol, HDL-cholesterol, triglycerides) and blood glucose were assayed in serum samples by enzymatic reaction methods using an automatic analyzer (ILab 350, Instrumentation Laboratory, Milan, Italy) and quality control for lipids and glucose was obtained by two commercial standards SeraChem® 1 (a control for normal levels) and SeraChem® 2 (a control for pathological high levels); the coefficients of variability (CV) of these two commercial standards were respectively 4.9% and 5.2% for blood total cholesterol; 3.2% and 3% for HDL-cholesterol; 5.2% and 5.3% for triglycerides, 4.7% and 4.1% for blood glucose.

High sensitivity C reactive protein (CRP) was measured in fresh serum samples by a particle-enhanced immune-turbidimetric assay (ILab 350, Instrumentation Laboratory, Milan, Italy). Quality control for CRP was maintained using in-house serum pool and commercial laboratory standard; inter-day coefficients of variability for CRP were 5.5% and 4.2%.

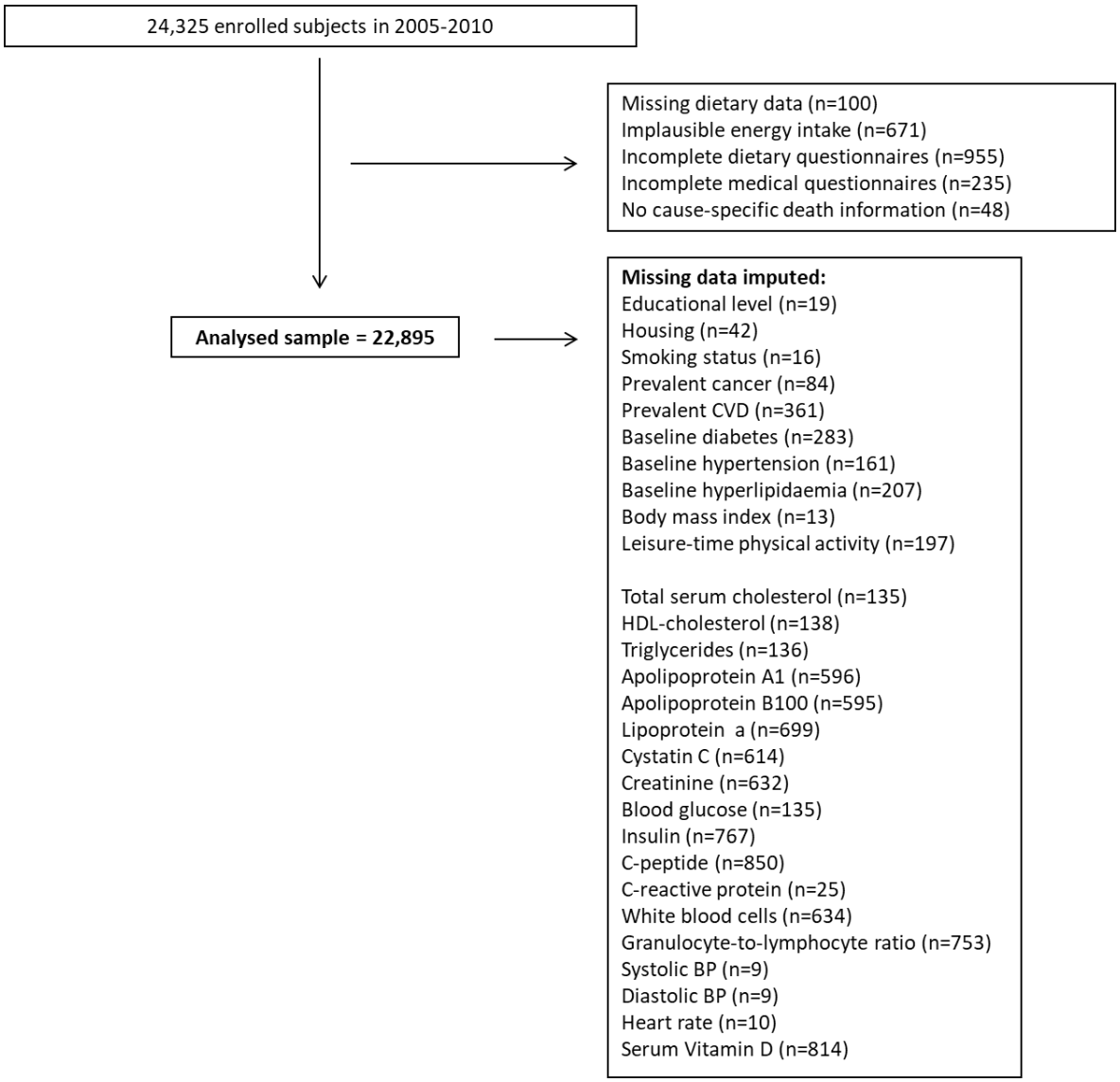
Hemocromocytometric analysis was performed by cell count (Coulter HMX, Beckman Coulter, IL Milan, Italy) within 3 h from blood collection. Quality control was performed by using three different levels of standards Abnormal 1 a pathologically high control (Abn1), Abnormal 2 (Abn2) a pathologically low control and Normal (Coulter HMX, Beckman Coulter). Coefficient of variability for white blood cells (WBC) was 6.2%, 3.3%, and 3.0% for Abn I, Abn II and Normal, respectively.

Apolipoprotein A1 (ApoA), apolipoprotein B100 (ApoB100), Lipoprotein a (Lp(a), markers of renal function (Cystatin C, Creatinine), insulin, C-peptide and serum vitamin D, were measured subsequently on thawed samples stored frozen in liquid nitrogen at the Biological bank of the Moli-sani Study, in the framework of the collaborative BiomarCaRE research project (EUFP7, HEALTH-F2-2011-278913) whose primary objective is to assess the value of established and emerging biomarkers for CVD risk prediction by using data from 23 cohorts across Europe (1).

References

1. Zeller T, Hughes M, Tuovinen T, Schillert A, Conrads-Frank A, Ruijter Hd, Schnabel RB, Kee F, Salomaa V, Siebert U, Thorand B, Ziegler A, Breek H, Pasterkamp G, Kuulasmaa K, Koenig W, Blankenberg S. BiomarCaRE: rationale and design of the European BiomarCaRE project including 300,000 participants from 13 European countries. Eur J Epidemiol. 2014;29:777-90.

Supplementary Figure A. Flowchart for selection of study participants from the Moli-sani Study, 2005-2010.



Supplementary Table A. Values of the Food Standards Agency nutrient profiling system (FSAm-NPS) score for each food/beverage used to compute the FSAm-NPS Dietary Index at individual level in the Moli-sani Study cohort (n=22,895)

Food labelled A	FSAm-NPS score
Broad beans in soup	-13
Peas in soup	-13
Peas	-12
Broccoli	-12
Beans in soup	-12
Beans or chickpeas	-11
Mushrooms	-11
Cabbage	-11
Chickpeas in soup	-11
Lentils in soup	-11
Kale	-10
Artichokes, fennels, celery	-10
Brussels sprouts	-9
Cauliflower	-9
Lettuce	-8
Eggplant, zucchini, green beans	-8
Red beet	-8
Raw peppers	-7
Artichokes or fennels or celery	-7
Raw carrots	-7
Potato	-7
Cooked carrots	-7
Savoy cabbage	-7
Turnip cabbage	-7
Cooked peppers	-7
Kiwi	-7
Egg/fresh pasta	-6
Tomato sauce	-6
Vegetables soup	-6
Legumes soup	-6
Tomatoes - in season	-6
Tomatoes - out of season	-6
Cooked onion	-6
Pear	-6
Orange	-6
Peach	-6
Apricot	-6
Strawberry	-6
Pasta in vegetables soup	-5
Stewed white meat	-5
Raw onion	-5
Apple	-5
Bananas	-5
Melon	-5
Olive	-5
Kaki	-5
Fig	-5
Cherry	-5
Pasta	-4
Roasted white meat	-4
Slice of white meat	-4

Chicken/turkey breast	-4
Mussels, clams	-4
Hake, dogfish, cod	-4
Trout	-4
Other type of fish	-4
Mandarin orange	-4
Grapes	-4
Plum	-4
Stewed red meat	-3
Roast beef	-3
Cutlets (white meat)	-3
Slice of red meat	-3
Bush/horse meat	-3
Liver	-3
Shrimp	-3
Squid, octopus	-3
Flounder, sole	-3
Tuna, salmon, swordfish	-3
Pumpkin	-3
Breakfast cereals	-3
Sliced pizza	-2
Cutlets (red meat)	-2
White meat steak	-2
Hamburger white meat	-2
Hamburger red meat	-2
Chicken/turkey leg	-2
Rabbit meat	-2
Pilchard, anchovy	-2
Nuts	-2
Low-fat yoghurt	-2
Stuffed pasta	-1
Meat sauce	-1
Rice	-1
Other risotto	-1
Polenta	-1
Restaurant pizza	-1
Homemade pizza	-1
Boiled meat	-1
Red meat steak	-1
Pork	-1
Fruit salad	-1
Other type of bread	-1
Semi-skimmed milk	-1
Semi-skimmed caffelatte	-1
Rusks	-1
Canned fruit	-1
Food labelled B	
Turkey/chicken meatballs	0
Chicken/turkey other parts	0
Eggs	0
Sandwiches with vegetables	0
Buns	0
Whole grain bread	0
Cappuccino	0
Caffelatte	0
Tea	0

Whole yogurt	0
Dried fruit	1
Lamb	1
White wine	1
Red wine	1
Rice salad	2
Meatballs (red meat)	2
Flans or potpies	2
Omelette	2
White bread (artisanal)	2
Orange juices	2
Whole milk	2
Decaffeinated coffee	2
Espresso	2
Percolated (mocha) coffee	2
Other type of coffee	2
Croquettes and fried arancini	2
Rose wine	2
Food labelled C	
Risotto	3
Offal	3
Canned fish	3
Fruit yoghurt	3
Other type of added fat	3
Stock cubes	4
Vegetables in oil	5
Meat soup	6
Pickled vegetables	6
Beer	6
Vegetable oil	6
Olive oil	7
Puddings	8
Ricotta	8
Mozzarella	9
Jam	10
Food labelled D	
Salt cod	11
Philadelphia cheese	11
Breadsticks, crackers	11
Stuffed cream	11
Ham	12
Stracchino cheese	12
Ice-cream	12
Other sauces	13
Grated cheese	13
Sandwiches with sliced salami	13
Dried beef	13
Parmesan	13
Soft drink	13
Honey	13
Canned meat	14
Fontina	14
Sugar	14
Biscuits	14
Candies	14
Artificial sweeteners	14

Cured ham	15
Emmenthal cheese	16
Other type of soft cheese	16
Spirits	16
Other animal fat	16
Fruit juices	17
Pastries	17
Other types of seasoned cheese	18
Sliced cheese	18
Taleggio cheese	18
Robiola cheese	18
Brioches, croissants	18
Pie	18
Butter	18
Food labelled E	
Pecorino cheese	19
Caciocavallo cheese	19
Blue cheese/gorgonzola	19
Mayonnaise	20
Sandwiches with cheese	20
Other processed meat	20
Alcoholic drinks	20
Mortadella, frankfurter	21
Margarines	21
Dry pastry	22
Bacon	24
Nut spread	24
Chocolate	24
Sausage	25
Salami	25

Supplementary Table B. Contribution (percentage) of each food group to total amount of ultra-processed foods consumed in the Moli-sani Study cohort (n=22,895)

Food groups (n=22)	1 serving (g)	Daily amount consumed (g/d)		Contribution to total UPF intake (%)
		Means	SD	
Processed meat	70	24.2	18.0	17.5
Cakes, pies, pastries, puddings (non-milk based)	60	25.6	32.1	14.2
Fruit drinks	125	26.8	57.3	11.0
Pizza (not homemade)	150	16.7	21.0	10.4
Ice-cream	75	12.5	14.9	8.1
Crispbread/rusks	8	8.2	11.7	6.8
Fruit yoghurts	125	14.2	37.7	6.0
Carbonated/soft/isotonic drinks, diluted syrups	200	16.3	62.7	5.4
Dry cakes, biscuits	6	8.1	12.9	5.0
Snacks	127	6.0	10.0	3.7
Stock cube	10	4.4	10.5	3.2
Chocolate	20	4.1	6.9	2.5
Breakfast cereals	30	2.5	8.5	1.5
Spirits, brandy	40	2.4	8.3	1.4
Spreadable cheese	50	1.9	4.7	1.2
Nut spread	25	1.1	3.6	0.5
Confectionery non chocolate	30	0.7	3.1	0.5
Sliced cheese	25	0.4	1.4	0.3
Margarine	0.2	0.3	0.3	0.2
Salty biscuits, aperitif biscuits, crackers	12.5	0.4	2.3	0.2
Mayonnaise and similar	14	0.3	1.1	0.2
Artificial sweeteners	1	0.1	0.5	0.1

Contribution (%) of each food group to the total consumption of ultra-processed food was calculated by dividing the amount (g/d) of each food group by the total amount of ultra-processed foods (g/d) multiplied by 100.

Supplementary Table C. Multivariable-adjusted linear regression models for the association between the Food Standards Agency nutrient profiling system (FSAm-NPS) dietary index and blood biomarkers and established CVD risk factors in the Moli-sani Study cohort (n=22,895) using data obtained from multiple imputation.

	FSAm-NPS dietary index			
Risk factors	Regression coefficient β ($x10^{-2}$)	Lower 95%CI ($x10^{-2}$)	Upper 95%CI ($x10^{-2}$)	P- value
Biomarkers of renal function[1]				
Cystatin C, mg/L	0.24	-0.02	0.49	0.07
Creatinine, mg/dL	0.17	-0.07	0.40	0.2
Biomarkers of glucose metabolism[1]				
Blood glucose, mg/dL	-0.1	-0.3	0.1	0.3
Insulin, pmol/L	1.4	0.8	2.1	<0.001
C-peptide, ng/mL	1.1	0.4	17	<0.001
Biomarkers of lipid metabolism				
Total blood cholesterol, mg/dL	-61	-120	-3	0.04
HDL-cholesterol, mg/dL	-15	-34	4	0.1
Triglycerides, mg/dL [1]	-1.2	-1.8	-0.5	<0.001
Apolipoprotein A1, g/L	0.2	-0.2	0.6	0.4
Apolipoprotein B100, g/L	-0.1	-0.5	0.2	0.5
Lipoprotein a, mg/dL	-34	-65	-3	0.03
Inflammatory biomarkers				
C reactive protein, mg/L[1]	1.7	0.4	3.0	0.009
White blood cell count, $x10^9$/L[1]	0.8	0.5	1.2	<0.001
Granulocyte-to-lymphocyte ratio	2.9	1.6	4.3	<0.001
Cardiovascular risk factors				
Systolic blood pressure, mmHg	-51	-30	20	0.7
Diastolic blood pressure, mmHg	13	5	26	0.04
Heart rate, bpm	10	-4	24	0.2
Serum Vitamin D, ng/mL	-13	-26	0	0.05

Multivariable model adjusted for sex, age (continuous), energy intake (continuous), educational level (categorical), housing tenure (categorical), smoking (categorical), BMI (continuous), leisure-time physical activity (continuous), history of cancer (no/yes), history of cardiovascular disease (no/yes), diabetes (no/yes), hypertension (no/yes), hyperlipidaemia (no/yes), and residence (categorical). Biomarkers were measured in serum blood samples.

[1] Logarithm

Supplementary Table D. Multivariable-adjusted linear regression models for the association between ultra-processed food intake (weight ratio) and blood biomarkers and established CVD risk factors in the Moli-sani Study cohort (n=22,895) using data obtained from multiple imputation.

	Ultra-processed food intake			
Risk factors	Regression coefficient β ($x10^{-2}$)	Lower 95%CI ($x10^{-2}$)	Upper 95%CI ($x10^{-2}$)	P- value
Biomarkers of renal function[1]				
Cystatin C, mg/L	1.2	0.9	1.4	<0.001
Creatinine, mg/dL	0.5	0.3	0.7	<0.001
Biomarkers of glucose metabolism[1]				
Blood glucose, mg/dL	-0.9	-1.1	-0.6	<0.001
Insulin, pmol/L	1.9	1.3	2.6	<0.001
C-peptide, ng/mL	1.4	0.7	2.0	<0.001
Biomarkers of lipid metabolism				
Total blood cholesterol, mg/dL	-237	-294	-179	<0.001
HDL-cholesterol, mg/dL	-87	-106	-69	<0.001
Triglycerides, mg/dL [1]	-0.9	-1.5	-0.2	0.01
Apolipoprotein A1, g/L	-1.6	-2.1	-1.2	<0.001
Apolipoprotein B100, g/L	-0.9	-1.2	-0.6	<0.001
Lipoprotein a, mg/dL	-38	-71	-5	0.02
Inflammatory biomarkers				
C reactive protein, mg/L[1]	2.2	0.9	3.5	<0.001
White blood cell count, $x10^9$/L[1]	0.5	0.1	0.8	0.005
Granulocyte-to-lymphocyte ratio	2.1	0.8	3.4	0.002
Cardiovascular risk factors				
Systolic blood pressure, mmHg	-45	-69	-20	<0.001
Diastolic blood pressure, mmHg	-22	-35	-9	0.001
Heart rate, bpm	29	15	43	<0.001
Serum Vitamin D, ng/mL	1.3	-1.2	14.0	0.8

Multivariable model adjusted for sex, age (continuous), energy intake (continuous), educational level (categorical), housing tenure (categorical), smoking (categorical), BMI (continuous), leisure-time physical activity (continuous), history of cancer (no/yes), history of cardiovascular disease (no/yes), diabetes (no/yes), hypertension (no/yes), hyperlipidaemia (no/yes), and residence (categorical). Biomarkers were measured in serum blood samples.

[1] Logarithm

Supplementary Table E. All-cause and cardiovascular mortality risk estimates associated with blood biomarkers and established CVD risk factors (1-unit increase) in the Moli-sani Study cohort (n=22,895) from multivariable-adjusted COX regression model including the FSAm-NPS dietary index as covariate, using data obtained from multiple imputation.

	All-cause mortality				**Cardiovascular mortality**			
	Hazard ratio (95%CI)	Lower 95%CI	Upper 95%CI	p-value	Hazard ratio (95%CI)	Lower 95%CI	Upper 95%CI	p-value
Insulin, pmol/L; (logarithm)	1.12	1.02	1.22	0.02	0.96	0.82	1.12	0.6
C-peptide, ng/mL; (logarithm)	1.24	1.12	1.37	<0.001	1.12	0.96	1.32	0.2
Total blood cholesterol, mg/dL	0.998	0.997	0.999	<0.001	0.998	0.996	1.000	0.05
Triglycerides, mg/dL; (logarithm)	0.97	0.88	1.07	0.5	0.95	0.80	1.11	0.5
Lipoprotein a, mg/dL	1.00	1.00	1.00	0.9	1.00	1.00	1.01	0.2
C reactive protein, mg/L; (logarithm)	1.17	1.12	1.22	<0.001	1.19	1.10	1.27	<0.001
White blood cell count, $x10^9$/L; (logarithm)	1.37	1.15	1.62	<0.001	1.74	1.30	2.32	<0.001
Granulocyte-to-lymphocyte ratio	1.11	1.10	1.13	<0.001	1.14	1.11	1.17	<0.001
Diastolic blood pressure, mmHg	1.01	1.00	1.01	0.02	1.01	1.00	1.02	0.006
Serum Vitamin D, ng/mL	0.98	0.98	0.99	<0.001	0.988	0.978	0.998	0.02

Multivariable model adjusted for sex, age (continuous), energy intake (continuous), educational level (categorical), housing tenure (categorical), smoking (categorical), BMI (continuous), leisure-time physical activity (continuous), history of cancer (no/yes), history of cardiovascular disease (no/yes), diabetes (no/yes), hypertension (no/yes), hyperlipidaemia (no/yes), residence (categorical), and the FSAm-NPS dietary index (continuous).

Supplementary Table F. All-cause and cardiovascular mortality risk estimates associated with blood biomarkers and established CVD risk factors (1-unit increase) in the Moli-sani study cohort (n=22,895) from multivariable-adjusted COX regression model including ultra-processed food intake as covariate, using data obtained from multiple imputation.

	All-cause mortality				**Cardiovascular mortality**			
	Hazard ratio (95%CI)	Lower 95%CI	Upper 95%CI	p-value	Hazard ratio (95%CI)	Lower 95%CI	Upper 95%CI	p-value
Cystatin C, mg/L (logarithm)	3.35	2.77	4.06	<0.001	3.27	2.41	4.43	<0.001
Creatinine, mg/dL (logarithm)	2.00	1.64	2.43	<0.001	1.86	1.37	2.54	<0.001
Blood glucose, mg/dL (logarithm)	1.44	1.14	1.81	0.002	1.43	0.97	2.11	0.07
Insulin, pmol/L (logarithm)	1.11	1.01	1.21	0.03	0.95	0.81	1.11	0.5
C-peptide, ng/mL (logarithm)	1.23	1.11	1.35	<0.001	1.10	0.94	1.30	0.2
Total blood cholesterol, mg/dL	0.998	0.997	0.999	<0.001	0.998	0.996	1.000	0.07
HDL-cholesterol, mg/dL	0.998	0.995	1.001	0.2	0.999	0.993	1.004	0.7
Triglycerides, mg/dL (logarithm)	0.97	0.88	1.06	0.5	0.94	0.80	1.11	0.5
Apolipoprotein A1, g/L	1.02	0.89	1.17	0.8	1.09	0.86	1.38	0.5
Apolipoprotein B100, g/L	0.86	0.72	1.03	0.1	0.93	0.68	1.26	0.6
Lipoprotein a, mg/dL	1.00	0.998	1.00	0.8	1.000	0.999	1.001	0.2
C-reactive protein, mg/L (logarithm)	1.16	1.11	1.22	<0.001	1.18	1.10	1.27	<0.001
White blood cell count, $x10^9$/L (logarithm)	1.35	1.14	1.60	<0.001	1.72	1.29	2.29	<0.001
Granulocyte-to-lymphocyte ratio	1.11	1.09	1.13	<0.001	1.14	1.11	1.16	<0.001
Systolic blood pressure, mmHg	1.00	1.00	1.01	0.007	1.01	1.00	1.01	<0.001
Diastolic blood pressure, mmHg	1.00	1.00	1.01	0.02	1.01	1.00	1.02	0.006
Heart rate, bpm	1.02	1.01	1.02	<0.001	1.02	1.01	1.02	<0.001

Multivariable model adjusted for sex, age (continuous), energy intake (continuous), educational level (categorical), housing tenure (categorical), smoking (categorical), BMI (continuous), leisure-time physical activity (continuous), history of cancer (no/yes), history of cardiovascular disease (no/yes), diabetes (no/yes), hypertension (no/yes), hyperlipidaemia (no/yes), residence (categorical), and ultra-processed food intake (weight ratio; continuous).

Supplementary Table G. Associations of the Food Standards Agency nutrient profiling system (FSAm-NPS) dietary index and ultra-processed food (UPF) consumption with blood biomarkers and established CVD risk factors in the Moli-sani Study cohort (n=22,895).

				FSAm-NPS dietary index			**UPF**					
				Change in risk factor			Change in risk factor					
Risk factors	Mean*	95%CI	SD	β_1[a] ($x10^{-2}$)	SE ($x10^{-2}$)	p-value[b]	β_2[a] ($x10^{-2}$)	SE ($x10^{-2}$)	p-value[b]	β ratio = β_1/β_2	Lower 95%CI	Upper 95%CI
C reactive protein (mg/L)[1]	1.51	1.49-1.53	-	2.9	0.7	<0.001	0.3	0.7	0.7	10	-56	76
White blood cell count ($x10^9$/L)[1]	6.02	6.00-6.04	-	1.0	0.2	<0.001	0.2	0.2	0.2	5	-5	15
Granulocyte/Lymphocyte ratio	2.01	-	0.92	3.1	0.7	<0.001	2.6	0.7	<0.001	1.0	0.1	1.9
Blood glucose (mg/dL)[1]	99.0	98.7-99.2	-	-0.8	0.1	<0.001	-1.4	0.1	<0.001	1.0	0.7	1.3
Insulin (pmol/L)[1]	51.9	51.6-52.3	-	1.6	0.4	<0.001	0.7	0.4	0.04	2.0	0.2	3.8
C-peptide (ng/mL)[1]	1.58	1.57-1.59	-	1.4	0.4	<0.001	0.3	0.4	0.4	3.3	-5.8	12
Blood cholesterol (mg/dL)	213	-	42	31	30	0.3	-230	30	<0.001	-0.1	-0.4	0.1
HDL-cholesterol (mg/dL)	58	-	15	-20	10	0.04	-74	10	<0.001	0.3	0.0	0.5
Triglycerides (mg/dL)[1]	4.7	-	0.5	-1.1	0.4	0.002	-1.6	0.4	<0.001	0.5	0.1	0.9
ApoA (g/L)	1.6	-	0.3	0.1	0.2	0.7	-1.3	0.2	<0.001	-0.1	-0.5	0.3
ApoB100 (g/L)	0.98	-	0.24	0.4	0.2	0.04	-0.9	0.4	<0.001	-0.4	-0.8	0.0
Lp(a) (mg/dL)	20	-	22	-46	16	0.004	-40	16	0.01	1.2	0.0	2.3
Cystatin C (mg/L)[1]	0.96	0.96-0.96	-	0.5	0.1	<0.001	1.3	0.1	<0.001	0.5	0.3	0.7
Creatinine (mg/dL)[1]	0.80	0.80-0.80	-	0.1	0.1	0.2	0.8	0.1	<0.001	0.1	-0.1	0.3
Systolic BP (mmHg)	141	-	21	-11	13	0.4	-58	13	<0.001	0.2	-0.3	0.6
Diastolic BP (mmHg)	82	-	10	23	6.8	<0.001	-27	7	<0.001	-0.9	-1.5	-0.2
Heart rate (bpm)	67	-	10	11	7.3	0.1	25	7	<0.001	0.4	-0.2	1.0
Serum Vitamin D (ng/mL)	19	-	9.3	-22	6.7	<0.001	-0.1	7	0.9	183	NC	NC

*Unadjusted means.

[1]Geometric means with corresponding 95% confidence intervals.

[a] Change for a 1-SD increase in the FSAm-NPS dietary index or ultra-processed food (weight ratio).

[b] P-values were obtained from linear regression models adjusted for sex, age, and energy intake.

NC, not calculable.

Supplementary Table H. Absolute Risk Difference (ARD, %) for the associations of ultra-processed food (UPF; weight ratio) and the Food Standards Agency nutrient profiling system (FSAm-NPS) dietary index as explanatory factors of their respective association with all-cause and cardiovascular disease (CVD) mortality.

	FSAm-NPS dietary index (Q4 vs Q1)	FSAm-NPS dietary index (Q4 vs Q1) + UPF (weight ratio; continuous)	UPF (Q4 vs Q1)	UPF (Q4 vs Q1) + FSAm-NPS dietary index (continuous)
	ARD % (95% CI)	ARD % (95% CI)	ARD % (95% CI)	ARD % (95% CI)
All-cause mortality	4.3 (1.4 to 7.2)	2.5 (-0.9 to 5.9)	9.7 (5.0 to 14.3)	11.6 (6.0 to 17.2)
CVD mortality	2.6 (0.3 to 4.9)	2.0 (-0.3 to 4.3)	5.0 (1.2 to 8.8)	6.4 (1.9 to 10.9)

Absolute risk difference obtained from a multivariable-adjusted model controlled for sex, age (continuous), energy intake (continuous), educational level (up to lower secondary, upper secondary, post-secondary), housing tenure (rent, 1 dwelling ownership, >1 dwelling ownership), smoking (never, current, former smokers), BMI (continuous), leisure-time physical activity (continuous), history of cancer (no/yes), history of CVD (no/yes), diabetes (no/yes), hypertension (no/yes), hyperlipidaemia (no/yes), and residence (urban, rural).

Supplementary Table I. Ultra-processed food (UPF; energy ratio) and the Food Standards Agency nutrient profiling system (FSAm-NPS) dietary index as explanatory factors of their respective association with all-cause and cardiovascular disease (CVD) mortality.

	FSAm-NPS dietary index (Q4 vs Q1)	FSAm-NPS dietary index (Q4 vs Q1) + UPF (continuous)			UPF (Q4 vs Q1)	UPF (Q4 vs Q1) + FSAm-NPS dietary index (continuous)		
	HR (95% CI)	HR (95%CI)	Attenuation		HR (95% CI)	HR (95%CI)	Attenuation	
			%	95%CI			%	95%CI
All-cause mortality	1.19 (1.04-1.35)	1.15 (1.00-1.31)	19.7	13.2 to 28.6	1.23 (1.07-1.40)	1.24 (1.08-1.42)	-4.5	-9.2 to -0.3
CVD mortality	1.32 (1.06-1.64)	1.27 (1.02-1.59)	11.7	6.0 to 19.9	1.33 (1.05-1.67)	1.33 (1.05-1.68)	-0.7	-6.4 to 4.4

Hazard ratios (HR) with 95% confidence interval (95%CI) obtained from multivariable cause-specific Cox proportional hazards regression models, using data obtained from multiple imputation (SAS PROC MI, followed by PROC MIANALYZE in SAS; n=10 imputed datasets).
The multivariable-adjusted model was controlled for sex, age (continuous), energy intake (continuous), educational level (up to lower secondary, upper secondary, post-secondary), housing tenure (rent, 1 dwelling ownership, >1 dwelling ownership), smoking (never, current, former smokers), BMI (continuous), leisure-time physical activity (continuous), history of cancer (no/yes), history of CVD (no/yes), diabetes (no/yes), hypertension (no/yes), hyperlipidaemia (no/yes), and residence (urban, rural).
Attenuation (%) represents the proportion of the FSAm-NPS dietary index (or UPF consumption) –mortality association explained by UPF as energy ratio (or by the FSAm-NPS dietary index), and was determined by calculating the percent attenuation in the β coefficient for the FSAm-NPS dietary index (or UPF intake; β_0) after inclusion of UPF (or the FSAm-NPS dietary index; β_1) to the multivariable-adjusted model as follows: $100 \times (\beta_0 - \beta_1)/(\beta_0)$.
95% CI around the percentage attenuation was obtained by using a bootstrap method with 1000 re-samplings.

Supplementary Table J. Sensitivity analyses for association of the Food Standards Agency nutrient profiling system (FSAm-NPS) dietary index with all-cause and cardiovascular (CVD) mortality and analysis of ultra-processed food (UPF; weight ratio) as an explanatory factor of these associations.

	All-cause mortality				**CVD mortality**			
	FSAm-NPS dietary index (Q4 vs Q1)	FSAm-NPS dietary index (Q4 vs Q1) + UPF (continuous)			FSAm-NPS dietary index (Q4 vs Q1)	FSAm-NPS dietary index (Q4 vs Q1) + UPF (continuous)		
	HR (95%CI)	HR (95%CI)	Attenuation		HR (95%CI)	HR (95%CI)	Attenuation	
			%	95%CI			%	95%CI
Overall (n=22,895)[a]	1.19 (1.04-1.35)	1.14 (1.00-1.31)	22.3	16.4 to 30.2	1.32 (1.06-1.64)	1.26 (1.01-1.58)	15.4	10.5 to 22.6
Exclusions								
Baseline CVD, cancer or diabetes (n=20,067)[b]	1.21 (1.03-1.41)	1.18 (1.00-1.39)	11.2	6.7 to 16.9	1.28 (0.97-1.70)	1.27 (0.96-1.69)	3.8	-0.8 to 9.8
Baseline hypertension, hypercholesterolemia or diabetes (n=15,353)[c]	1.20 (0.97-1.49)	1.15 (0.93-1.44)	21.8	12.3 to 36.2	1.08 (0.69-1.68)	1.00 (0.64-1.60)	85	-762 to 821

Hazard ratios (HR) with 95% confidence interval (95%CI) obtained from multivariable cause-specific Cox proportional hazards regression models, using data obtained from multiple imputation (SAS PROC MI, followed by PROC MIANALYZE in SAS; n=10 imputed datasets).

[a] The multivariable-adjusted model was controlled for sex, age (continuous), energy intake (continuous), educational level (up to lower secondary, upper secondary, post-secondary), housing tenure (rent, 1 dwelling ownership, >1 dwelling ownership), smoking (never, current, former smokers), BMI (continuous), leisure-time physical activity (continuous), history of cancer (no/yes), history of CVD (no/yes), diabetes (no/yes), hypertension (no/yes), hyperlipidaemia (no/yes), and residence (urban, rural).

[b] as in model [a] not including baseline history of cancer, history of CVD, diabetes.

[c] as in model [a] not including baseline hypertension, hypercholesterolemia, and diabetes.

Attenuation (%) represents the proportion of the FSAm-NPS dietary index –mortality association explained by UPF as weight ratio, and was determined by calculating the percent attenuation in the β coefficient for the FSAm-NPS dietary index (β_0) after inclusion of UPF (β_1) to the multivariable-adjusted model as follows: 100 x $(\beta_0 - \beta_1)/(\beta_0)$.

95% CI around the percentage attenuation was obtained by using a bootstrap method with 1000 re-samplings.

Supplementary Table K. Sensitivity analyses for association of ultra-processed food consumption (UPF; weight ratio) with all-cause and cardiovascular (CVD) mortality and analysis of the Food Standards Agency nutrient profiling system (FSAm-NPS) dietary index as an explanatory factor of these associations.

	All-cause mortality				**CVD mortality**			
	UPF (Q4 vs Q1)	UPF (Q4 vs Q1) + FSAm-NPS dietary index (continuous)			UPF (Q4 vs Q1)	UPF (Q4 vs Q1) + FSAm-NPS dietary index (continuous)		
	HR (95%CI)	HR (95%CI)	Attenuation		HR (95%CI)	HR (95%CI)	Attenuation	
			%	95%CI			%	95%CI
Overall (n=22,895)[a]	1.19 (1.05-1.36)	1.20 (1.05-1.37)	-3.3	-7.3 to 0.30	1.27 (1.02-1.58)	1.27 (1.02-1.59)	0.0	-5.0 to 4.9
Exclusions								
Baseline CVD, cancer or diabetes (n=20,067)[b]	1.12 (0.95-1.32)	1.13 (0.96-1.33)	-6.7	-16.5 to -0.5	1.11 (0.84-1.48)	1.12 (0.84-1.49)	-8.6	-56.5 to 2.1
Baseline hypertension, hypercholesterolemia or diabetes (n=15,353)[c]	1.21 (0.97-1.49)	1.21 (0.98-1.50)	-0.2	-7.3 to 7.1	1.29 (0.84-1.97)	1.33 (0.87-2.04)	-11.5	-30.5 to -3.7

Hazard ratios (HR) with 95% confidence interval (95%CI) obtained from multivariable cause-specific Cox proportional hazards regression models, using data obtained from multiple imputation (SAS PROC MI, followed by PROC MIANALYZE in SAS; n=10 imputed datasets).

[a] The multivariable-adjusted model was controlled for sex, age (continuous), energy intake (continuous), educational level (up to lower secondary, upper secondary, post-secondary), housing tenure (rent, 1 dwelling ownership, >1 dwelling ownership), smoking (never, current, former smokers), BMI (continuous), leisure-time physical activity (continuous), history of cancer (no/yes), history of CVD (no/yes), diabetes (no/yes), hypertension (no/yes), hyperlipidaemia (no/yes), and residence (urban, rural).

[b] as in model [a] not including baseline history of cancer, history of CVD, diabetes.

[c] as in model [a] not including baseline hypertension, hypercholesterolemia, and diabetes.

Attenuation (%) represents the proportion of the UPF–mortality association explained by the FSAm-NPS dietary index, and was determined by calculating the percent attenuation in the β coefficient for UPF intake (β_0) after inclusion of the FSAm-NPS dietary index (β_1) to the multivariable-adjusted model as follows: 100 x $(\beta_0 - \beta_1)/(\beta_0)$.

95% CI around the percentage attenuation was obtained by using a bootstrap method with 1000 re-samplings.

Moli-sani Study Investigators

The enrolment phase of the Moli-sani Study was conducted at the Research Laboratories of the Catholic University in Campobasso (Italy), the follow up of the Moli-sani cohort is being conducted at the Department of Epidemiology and Prevention of the IRCCS Neuromed, Pozzilli, Italy.

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Baseline Recruitment staff is available at https://www.moli-sani.org/?page_id=173